CHRONIC TOXICITY SUMMARY

METHYL t-BUTYL ETHER

(MTBE; 2-methoxy-2-methylpropane; tert-butyl methyl ether; methyl 1,1dimethyl ether)

CAS Registry Number: 1634-04-4

I. Chronic Toxicity Summary

Inhalation reference exposure level	**8000 mg/m^3 (2000 ppb)**
Critical effect(s)	Nephrotoxicity, prostration, periocular swelling in Fischer 344 rats
Hazard index target(s)	Kidney; eyes; alimentary system

II. Physical and Chemical Properties (HSDB, 1994)

Description	Colorless liquid
Molecular formula	$C_5H_{l2}0$
Molecular weight	88.15 g/mol
Density	0.7405 g/cm^3 @ 20°C
Boiling point	55.2°C @ 760 mm Hg
Vapor pressure	245 torr @ 20°C
Solubility	Soluble in alcohol, ether, and 5% soluble in water
Conversion factor	1 ppm = 3.61 mg/m^3 @ 25° C; 3.67 mg/m^3 @ 20° C

III. Major Uses or Sources

Methyl t-butyl ether (MTBE) is used as a gasoline additive to improve octane ratings and reduce emissions of some pollutants, in industry to improve miscibility of solvents, and in clinical medicine to dissolve cholesterol gall stones (Yoshikawa *et al.*, 1994). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California,based on the most recent inventory, were estimated to be 215,182 pounds of MTBE (CARB, 1999).

IV. Effects of Human Exposure

Gasoline (with 10% MTBE) tanker drivers reported significantly higher fatigue at the end of the work week than before the work week, and those with longer exposure to gasoline with MTBE during the work week reported significantly higher fatigue than drivers with shorter exposure

(Hakkola *et al*., 1997). 20% of drivers reported symptoms such as headache, dizziness, nausea, and dyspnoea at the end of work week. No human chronic toxicity or chronic epidemiology information for MTBE without coexposure to gasoline was found.

Ten healthy male volunteers undergoing light physical work were exposed to 5, 25, and 50 ppm MTBE vapor for 2 hours (Nihlen *et al*., 1998). While a solvent smell was noted at these concentrations, there were no consistent concentration-related effects on reported ocular or nasal irritation. The blockage index (a measure of nasal airway resistance) increased significantly after exposure but was not correlated with exposure concentration.

V. Effects of Animal Exposure

Male and female rats (50/sex/group) were exposed by inhalation for 6 hours/day, 5 days/week to mean concentrations of 0, 403, 3023, or 7977 ppm (0, 1453, 10,900, or 28,760 mg/m^3) MTBE for 24 months (Chun *et al.*, 1992). Clinical signs, hematology, body weights and food consumption were monitored. Necropsy included measurements of organ weights and histopathology. Corticosterone levels were measured on 10 animals prior to sacrifice. Serum enzymes were not monitored. The NOAEL for several endpoints, including non-alpha-2μ-globulin induced nephrotoxicity, increased relative liver and kidney weights and prostration in females, and periocular swelling in both sexes was 403 ppm (1453 mg/m^3).

Mice were exposed for 6 hours/day, 5 days/week for 18 months to MTBE concentrations of 0, 402, 3014, or 7973 ppm (0, 111, 835, or 2208 mg/m^3) (Burleigh-Flayer *et al.*, 1992). The mice exposed to the highest concentration (7973 ppm) all exhibited ataxia. Prostration was also noted in 8 of 50 animals in this group. Liver weights were elevated in a concentration-dependent manner in the female mice but this change was not significant at the lowest concentration (402 ppm). Kidney weights were elevated in the female mice exposed to 7973 ppm. At the highest concentration, a significant increase in hepatocellular hypertrophy and adrenal gland weight was detected in the male mice. Spleen weights were increased in the females exposed to the highest concentration.

Moser *et al*. (1998) exposed female B6C3F$_1$ mice to 7924 ppm (2195 mg/m^3) MTBE for 4 months, or 7919 ppm (2194 mg/m^3) MTBE for 8 months; controls received plain air. Body weight increases for control and MTBE-exposed mice, respectively, were 57% and 37% at 4 months and 79% and 45% at 8 months: the reduced weight gain in MTBE-exposed mice was significantly different from the controls at both time points. In MTBE-exposed mice, mean uterine weight was 83% reduced relative to controls at 4 and 8 months. Ovary weight was also reduced in exposed mice, the mean weight being 55% of control at 4 months and 51% of control at 8 months. Pituitary weights were decreased by 44% and 31% at 4 and 8 months, relative to controls. Disturbances of the estrus cycle and histological changes in the reproductive organs were also noted. Although the changes in organ weights and histology were suggestive of an anti-estrogenic effect of MTBE, serum estrogen levels were unaffected. No changes in estrogen receptor (ER) immunoreactivity in reproductive system tissues were observed. Experiments *in vitro* failed to demonstrate any inhibition of estradiol binding to ER by MTBE or its metabolites. No inhibition of ER by MTBE was detected, nor was there any inhibition of the induction of ER by estradiol. The authors concluded that the apparent anti-estrogenic effects of MTBE were not

mediated via the ER, and drew a parallel with the anti-estrogenic effects of dioxins and chlorinated biphenyls.

Tests for histopathology in the respiratory tract, plasma corticosterone levels, motor activity and neurobehavioral endpoints were performed in rats exposed to MTBE at concentrations of 0, 797, 3920, or 8043 ppm (0, 2877, 14151, or 29035 mg/m^3), 6 hours/day, 5 days/week for 13 weeks (Dodd and Kintigh, 1989). Of these endpoints, the most significant finding was an elevation in plasma corticosterone in the high dose group. This finding was consistent with the elevated adrenal weights reported by Burleigh-Flayer *et al.* (1992). A clear dose-response for neurotoxic effects in these rats was not established.Biles *et al.* (1987) reported a NOAEL of 300 ppm (1083 mg/m^3) MTBE for decreased pup viability in rats exposed for 6 hours/day, 5 days/week for a total of 16 weeks. Animals exposed to 1240 ppm (4470 mg/m^3) or 2860 ppm (10,311 mg/m^3) MTBE exhibited slightly decreased pup survival.

Neeper-Bradley (1991) exposed rats to 0, 402, 3019, or 8007 ppm (0, 111, 836, and 2218 mg/m^3) MTBE over 2 generations. Exposures were for 6 hours/day, 5 days/week during the prebreeding period, and for 7 hours/day, 5 days/week during gestation and lactation. Parental effects of MTBE exposure were observed, including ataxia, blepharospasm, lack of startle reflex, and increased relative liver weights (F1 generation only). There were no histological changes in the organs from either parental generation. Reduced body weights were observed in the F1 and F2 pups at the 3019 and 8007 ppm concentrations. Reduced survivability to postnatal day 4 was observed in the 8007 ppm group. No adverse effects were noted at the 403 ppm (111 mg/m^3) concentration.

In a developmental and reproductive toxicity study, Conaway and associates (1985) found no significant increases in maternal or fetal toxicity, nor in pregnancy rates or in any gross toxicologic parameter tested with pregnant rats or mice exposed during gestation to concentrations of MTBE up to 3300 ppm (11,897 mg/m^3).

Maternal toxicity, in the form of hypoactivity and ataxia, was observed in pregnant mice exposed during gestation to 4076 ppm (14,690 mg/m^3) MTBE (Bushy Run Research Center, 1989a). Significant reductions in food intake and body weight gain were observed in dams exposed to 8153 ppm (29,390 mg/m^3). Fetal body weight was significantly reduced in the 4076 ppm group, and there were significant increases in the incidences of skeletal variations and unossified phalanges in the 4076 and 8153 ppm groups. Pregnant rabbits exposed to similar concentrations during gestation showed no significant maternal or fetal toxicity or developmental toxicity up to a concentration of 8021 ppm (28,918 mg/m^3) (Bushy Run Research Center, 1989b).

VI. Derivation of Chronic Reference Exposure Level

Study	Chun *et al.*, 1992; Bird 1997
Study population	Male and female rats (50 per sex/group)
Exposure method	Discontinuous whole-body inhalation exposures (0, 403, 3023, or 7977 ppm)
Critical effects	Nephrotoxicity, increased liver and kidney

	weight, prostration and periocular swelling
LOAEL	3023 ppm
NOAEL	403 ppm
Exposure continuity	6 hours per day, 5 days per week
Exposure duration	24 months
Average experimental exposure	72 ppm for the NOAEL group
Human equivalent concentration	72 ppm for the NOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	2 ppm (2000 ppb, 8 mg/m^3, 8000 μg/m^3)

The USEPA (1995) based its RfC of 3000 μg/m^3 on the same study but included a Modifying Factor (MF) of 3 for database deficiencies. The criteria for use of modifying factors are not well specified by U.S. EPA. Such modifying factors were not used by OEHHA.

VII. Data Strengths and Limitations for Development of the REL

The major strengths of the REL for MTBE are the use of a comprehensive, long-term multiple dose study with large sample sizes and the observation of a NOAEL. The major uncertainty is the lack of human data.

VIII. References

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